

ABSTRACT

PPPM in Diabetes Care

GERMAN FEDERATION OF DIABETICS—STATEMENT

Hadder M

Deutscher Diabetiker Bund (German Federation of Diabetics),
Germany

Dear Ladies and Gentlemen,

As a representative of the German Federation of Diabetics (Deutscher Diabetiker Bund) in North Rhine-Westphalia I would like to communicate from the view of people being involved in the disease diabetes, how and to which scale Predictive, Preventive and Personalised Medicine in Germany has a chance to be integrated into the therapy of diseases.

Predictive Medicine

The German Federation of Diabetics believes that it is meaningful for people, living under the risk of suffering from a specific disease, to evaluate the risk factors more precisely by means of Predictive Medicine. On the other hand it might be ethically questionable to apply those methods in cases, in which serious consequences (e.g. death) can possibly be expected. For the patients this could be a situation of extraordinary mental stress. In those cases predictive methods or tests should only be applied, if a patient has given an explicit mandate. In our opinion results of such methods of testing should only be communicated to the patient by qualified medical specialists.

However, when we are talking about disease patterns, in which a patient's behaviour, in combination with a qualified therapy, could avoid a worsening of the disease, the chances of Predictive Medicine should be employed.

Prevention

Prevention is not only a problem in our public healthcare system but also a problem of our society in general. Despite the fact that every third teenager carries the risk of diabetes there is almost no effort in prevention. This is even worse

as genetic, family-related and socio-economic factors play a critical role in the further growing up of the adolescent persons. Hence prevention and working towards a healthy lifestyle should already start on the pre-school level, for example in the kindergarten or play school. The steadily increasing number of children and adolescents suffering from diabetes type 2 is significant. Normally information about the disease diabetes and a healthy lifestyle does not start before the manifestation of the disease took place. Especially for those patients, carrying a high risk, special risk-related measures of prevention should regularly be taken.

Personalised Medicine

The German Federation of Diabetics expects considerable success when Personalised Medicine is applied in the treatment of serious and/or chronic diseases. In Germany the influence of economic factors on political decisions on health care has been growing. The legislative organs and self-governing bodies impose strict regulations on doctors and therapists, which in most cases only allow standardised treatment.

However, from our point of view individual treatment by means of biomarkers provides a lot of advantages:

- Insufficient or even wrong treatment and therapies could be avoided
- Risks or adverse reactions of pharmaceuticals and therapies could be avoided or limited
- With individual treatment from the beginning, unnecessary cost for insufficient or wrong treatment could be eliminated
- Patients could be protected from significant complications of the disease and also from cost.

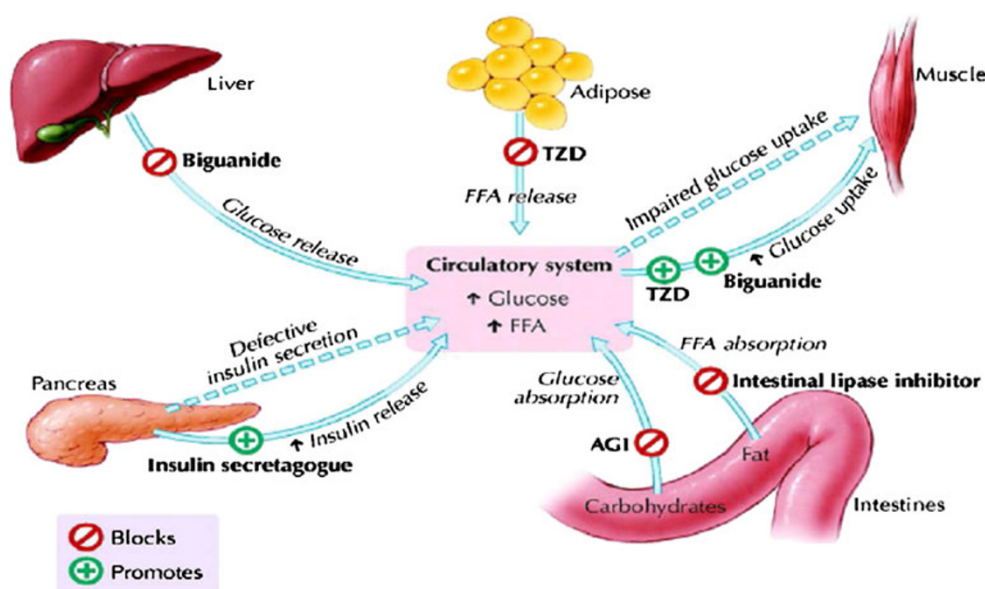
POTENTIAL NEW STRATEGIES IN DIABETES THERAPEUTICS

Sena CM

Institute of Physiology, IBILI, Faculty of Medicine,
University of Coimbra, Portugal

The rising incidence of diabetes, metabolic syndrome, and subsequent vascular diseases is a major public health problem in industrialized countries. Diabetes is a progressive disease with a complex pathophysiology that includes peripheral insulin resistance, declining β -cell function and mass, declining insulin secretion over time, inappropriate glucagon secretion and hepatic glucose production, and deficiencies in amylin and glucagon-like peptide (GLP-1). The main pharmacological drugs that have been used in the treatment of type 2 diabetes are: α -glucosidase

inhibitors, to delay intestinal carbohydrate absorption (e.g. acarbose); biguanides to target hepatic insulin resistance (e.g. metformin); insulin secretagogues or sulphonylureas, to increase pancreatic insulin secretion and also increase glucose-induced insulin secretion (e.g. glibenclamide; gliclazide); insulin sensitisers or thiazolidinediones, to target adipocyte and muscle insulin resistance (e.g. troglitazone; rosiglitazone); and intestinal lipase inhibitors, to inhibit fat absorption and promote weight loss in obese patients (e.g. orlistat) (Figure).



Observational studies have found that bariatric surgery is effective in patients with obesity and diabetes, reinstating near normal glycaemia in 50–80% of patients for several years. Bariatric surgery is now an accepted treatment for obese patients with diabetes. The finding that glycaemic control is promptly reinstated in most patients with diabetes when less food passes through the stomach, duodenum, and proximal jejunum—independently of the amount of weight lost—has focused attention on research into gastrointestinal factors as a potential source of new drugs for the treatment of type 2 diabetes. Several gastrointestinal peptides (including GLP-1, glucose dependent insulinotropic polypeptide, and peptide YY) could provide a basis for new treatments in patients with obesity and diabetes. DPP-4 inhibitors and GLP-1 agonists stimulate glucose-mediated insulin secretion from pancreatic β cells and suppress glucagon release; GLP-1 agonists also delay gastric emptying; and amylin agonists suppress glucagon release and delay gastric emptying. Combination therapy that includes drugs with complementary mech-

anisms of action is most effective and sometimes preferred.

There is great potential for developing a new generation of therapeutics that offer better control of diabetes, its co-morbidities and its complications. This contribution summarizes current pharmacological approaches to treat diabetes mellitus and will focus on novel therapies for diabetes mellitus that are under development. Potential new treatments include analogues of intestinal and adipocyte hormones, inhibitors of renal glucose reabsorption and cellular glucocorticoid activation, and activators of cellular energy production.

INDICES OF DNA DAMAGE AS POTENTIAL PREDICTIVE MARKERS OF DIABETIC NEPHROPATHY

Mozaffari MS, Yao Liu J, El-Awady A, Baban B

Department of Oral Biology, College of Dental Medicine, Georgia Health Sciences University, Augusta, Georgia 30912, USA

The world-wide epidemic of obesity has fueled the increasing incidence of type 2 diabetes mellitus. In turn, type 2 diabetes is associated with major target organ complications with increased morbidity and mortality. Indeed, nephropathy is a prominent complication of type 2 diabetes with end-stage renal failure which requires renal dialysis and/or renal transplantation. It is, therefore, imperative to identify novel diagnostic predictors for early detection, and monitoring progression, of target organ pathologies such as nephropathy. A hallmark feature of type 2 diabetes mellitus is hyperglycemia-induced oxidative stress and consequent DNA damage. Thus, identification of indices of DNA injury that co-relate with disease progression and manifestation of target organ pathologies are urgently needed. While the modified nucleoside, 8-hydroxydeoxyguanosine (8-OHdG), is a useful index of oxidative DNA damage, γ H2AX has emerged as a sensitive index of double-strand DNA (dsDNA) breaks, the most severe form of DNA injury. Accordingly, the focus of our recent studies was to examine the impact of insulin resistance/type 2 diabetes mellitus on urinary and/or renal tissue 8-OHdG and γ H2AX utilizing two highly relevant animal models of the disease, namely the obese Zucker rat (OZR) and db/db mouse (and their respective lean nondiabetic controls, LZR and db/m, respectively); these animal models lack the leptin receptor and thus are markedly obese, insulin resistant and hyperglycemic. The OZR displayed mild hyperglycemia but marked hyperinsulinemia in association with increased albuminuria compared to the lean controls. Urinary excretion of 8-OHdG was significantly increased in the OZR compared to LZR. Interestingly, however, renal tissue of OZR revealed similar 8-OHdG immunostaining intensity and pattern to that of LZR. Subsequent studies using the severely hyperglycemic obese diabetic db/db mice revealed significant reduction in glomerular function but marked albuminuria than their lean db/m controls. Further, urinary excretion of 8-OHdG was markedly increased in db/db, than db/m, group while renal tissue 8-OHdG immunostaining was similar between the two groups. On the other hand, renal tissue of db/db mice displayed increased nuclear γ H2AX immunostaining compared to the db/m group. Subsequent Western blot analysis further confirmed increased renal tissue γ H2AX level in db/db mice. Collectively, the results suggest that while urinary 8-OHdG excretion is a helpful predictive marker of whole body oxidative DNA damage, renal tissue 8-OHdG immunostaining is an unlikely predictor of local oxidative DNA damage. On the other hand, renal tissue γ H2AX is a more likely predictor of local DNA injury.

Supported by a grant from the National Institutes of Health.

RETINOPATHY SCREENING AS THE PROMOTER OF PREDICTIVE, PREVENTIVE AND PERSONALISED MEDICINE IN TYPE 2 DIABETES CARE

Salminen L

School of Medicine, University of Tampere, Finland

More than 75 % of patients who have diabetes mellitus for more than 20 years develop a kind of diabetic retinopathy (DR). In cohort studies, DR is prevented and treated effectively by strict control of HbA1c, hypertension and hypercholesterolaemia by lifestyle changes and medication. In clinical practice, DR is one primary endpoint and maker of suboptimal quality of diabetes treatment. DR is a leading cause of visual impairment in working population. However, diabetes related vision loss is greatest in the elderly with type 2 diabetes (T2D). Digital fundus photography by accredited workforce, image grading, quality assurance and IT considerations is the evidence based, sensitive and specific method for DR screening and follow up. It is one of the most cost effective health procedures to promote timely treatment of patients with T2D from a public health standpoint.

European countries differ considerably in type and quality of T2D as well as DR prevention and treatments. It is assumed that few countries have been able to increase resources for eye health since Liverpool Declaration in 2005 (www.drscreening2005.org.uk). This contribution is focused on numerical facts of T2D in Europe with incidence and prevalence, prevention and care models. Factors like personal health practices (exercise, self-care), psychosocial (social support, internal locus of control), and healthcare use (access to care, type of care provided, belief in the ability of the healthcare system to help), diabetes registries, mass implication of preventive guidelines and programs, electronic patient records with digital images are identified and outlined and road mapped. The unique opportunity of ophthalmologists to influence patient behavior and inform patient's primary care physician is stressed. It is suggested that information technology and social media will play a central role in the redesign of the healthcare quality promoting predictive, preventive and personalized medicine for patients with T2D.

VISUAL LOSS IN DIABETIC PATIENTS—DO WE PREVENT IT OR DO WE TREAT ONLY THE COMPLICATIONS?

Josifova T, Henrich PB, Cybulska A, Flammer J

University Hospital Basel, Eye Clinic

There are two main reasons of visual loss in patients with diabetes: diabetic maculopathy (DM) and proliferative diabetic retinopathy (PDR). The prevalence of

PDR and DME is closely related to the duration of diabetes. During a life-time more than 50% of patients with type 2 diabetes develop visual loss, versus 1/3 of patients with type 1 diabetes. Correlation between blood glucose and presence of PDR, in absence of C peptide determination is in close connection to the development of retinopathy. Two initial therapeutic approaches are up to date in the treatment of PDR. The aim of the first one is to discourage proliferations, and second—to prevent and relieve the contraction of the fibroproliferative vitreoretinal membranes (Fig. 1). Laser photocoagulation (LFK)—retinal burns is still the “golden standard” in prevention and treatment of PDR. Destruction of the new vessels required burns involve the full thickness retina and often lead to nerve fiber field defects. Although being treated with LFK, some of the patients develop severe complications and underwent surgical procedure. Recovery of good vision after surgery in PDR in the early vitrectomy group is observed only in 24.5% of the patients. The prevalence of DM in type 2 diabetes after 5 years duration is about 5% compared to 20% after 20 years of duration. The classification of DM is: diabetic macular edema (DME), ischaemic maculopathy and vitreomacular interface changes. Improving the diagnostic techniques, a lot of ongoing studies have investigated different medications for intravitreal usage in conditions of DME (Fig. 2). The grid LFK on the leaking microaneurysms in combination with focal LFK is still one of the important treatments of DME. Up to date medications include the corticosteroids and Anti-VEGF drugs. A lot of studies such as READ (Resolve, Restore and DRCR.net Study Group) have summarised the latest results. Improvement in findings does not always match to visual acuity increase. The treatment of the vitreomacular interface changes is surgical, but without great improvement, and the changes are recurrent. There is no effective treatment for ischemic macular changes, which are always associated with severe visual loss. Despite a lot of investigations run, there is still no any protocol elaborated for DME treatment.

Considering the fact that about 26% of patients with type 1 and 36% type 2 diabetic patients have never had their eyes examined, the risk for different ocular complications is very high: 32% of patients with diabetes at high-risk for visual loss never undergo an eye examination. When examined almost 61% of these patients are found to have diabetic retinopathy, cataract, glaucoma or other ocular pathologies. In order to prevent the ocular diabetic complications,

healthcare and eye-care delivery system on a personal-based level should be enhanced in societies. The only key to success: focusing on “individuals” but not on “patients” with already manifested disorders to apply innovative investigation approaches in the general population and groups at risk.



Fig. 1 Fundus foto of a PDR with preretinal haemorrhage

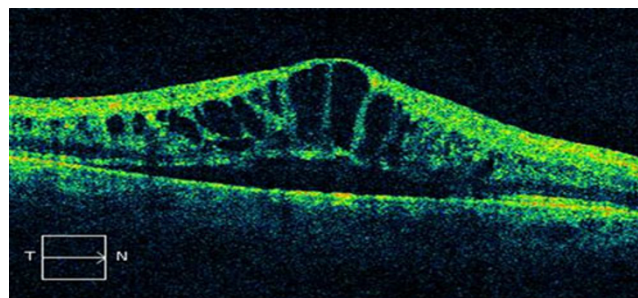


Fig. 2 OCT finding of DME

ANKLE—BRACHIAL INDEX IN TYPE 2 DIABETES PATIENTS AND CARDIOVASCULAR RISK

Nussbaumerova B, Rosolova H, Sefrna F, Sipova I, Sifalda P
2nd Medical Department, Charles University in Prague—
Medical Faculty in Pilsen, Czech Republic

Purpose: The ankle—brachial index (ABI), i.e. the ratio of systolic blood pressure (SBP) measured on the ankle and on the arm, is considered the diagnostic parameter for the

peripheral occlusive artery disease and the marker of cardiovascular (CV) risk. We measured ABI in patients with type 2 diabetes (DM2) and evaluated its impact on the CV risk. Method: A sample of 253 DM2 patients (135 males, 118 females, average age 66 ± 9 y.) was examined. The supine ankle SBP was measured with the Doppler ultrasonography sond after a 5 minutes rest, with the 2 mmHg accuracy, SBP on the identical arm was measured the same way with the same accuracy by the mercury sphygmomanometer. The $ABI < 0.9$ suggests the arterial occlusion, on the contrary the $ABI \geq 1.2$ is nondiagnostic and suspected of mediocalcinosis. The CV risk was evaluated according to up-to-date guidelines; as the high risk patients were considered the patients with manifested CV diseases (information from the patients' documentation), with elevated coronary calcium score (CAC) evaluated by the Agatston's score (101–400 high risk, ≥ 401 very high risk) or according to the global CV Risk Score $\geq 5\%$. Used statistical method: Wilcoxon's unpaired test, χ^2 test, Spearman's correlation, multiple logistic regression.

Results: The $ABI < 0.9$ was found unilateral in 20 DM2 (8 %), bilateral in 27 (11%), thus the ABI was decreased in 47 (19%) DM2. Other 168 DM2 (66%) showed the normal ABI and 38 (15%) the nondiagnostic ABI. There was no significant difference in the characteristics of DM2 patients with the normal and the nondiagnostic ABI. The DM2 patients with the $ABI \leq 0.9$ compared to the rest of the sample were older males with elevated total cholesterol, total homocystein and CAC and with the history of CV diseases. Many CV and metabolic risk factors correlated significantly positively with $ABI < 0.9$: age, glycaemia, total homocystein, CAC ($p < 0.05$), LDL-cholesterol ($p < 0.01$) and SBP ($p < 0.01$). The $ABI < 0.9$ was significantly and independently associated with age ($p < 0.001$), smoking ($p < 0.01$), LDL-cholesterol, total homocystein and CAC ($p < 0.05$). The decreased ABI was a strong significant predictor of ischemic stroke and symptomatic carotid stenosis for the next 3 years ($p < 0.001$). The $ABI < 0.9$ correlated significantly neither with ultrasensitive C-reactive protein nor with presence of the metabolic syndrome in DM2.

Conclusion: Decreased $ABI < 0.9$ was found in 19% of DM2 patients. It was in a significant and independent association with age, smoking, LDL-cholesterol, total homocystein and CAC. We evaluated $ABI < 0.9$ as a strong predictor of ischemic stroke and symptomatic carotid artery stenosis. That is why these patients need an individual, complex and intensive intervention. Nondiagnostic ABI values were found in 15% of the sample; a high prevalence of mediocalcinosis in DM2 patients is suspected.

CHARACTERISTICS OF INFLAMMATION COMMON TO BOTH DIABETES AND PERIODONTITIS: ARE PREDICTIVE DIAGNOSIS AND TARGETED PREVENTIVE MEASURES POSSIBLE?

Krishna R¹, Hanes PJ²

¹Department of Periodontics, Georgia Health Sciences University, College of Dental Medicine, Augusta, GA 30912, USA

²Academic Affairs, Georgia Health Sciences University, College of Dental Medicine, Augusta, GA 30912, USA

In 2001, an NIH workgroup standardized the definition of a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”.

Diabetes has several effects on the oral cavity including xerostomia, burning mouth, altered wound healing, and increased incidence of periodontal diseases such as gingivitis and periodontitis. Diabetes and periodontitis are chronic inflammatory disorders that contribute to each others' severity and worsen each others' prognosis. Studies have shown that patients with diabetes are at increased risk of developing periodontitis, and that diabetics with untreated periodontitis have more difficulty controlling serum glucose. Although the primary etiology of periodontal disease is the bacterial biofilm that is present on the surface of the teeth, 50% of the tissue destruction is attributed to host response.

Epidemiologic studies have shown a three to fourfold increased risk for progressive periodontal destruction in diabetic patients compared with individuals without diabetes. The factors suggested to explain this relationship include altered immunoinflammatory response to bacterial pathogens, diminution of the formative aspects of connective tissue metabolism, impaired wound healing, microvascular changes, and formation of advanced glycation end-products. Periodontal treatment that reduces gingival inflammation aids in the control of hyperglycemia. Immune cell functions such as adherence, chemotaxis and phagocytosis, and monocytes/macrophage cell line that is hyper-responsive to bacterial antigens resulting in increased production of pro-inflammatory cytokines IL-1 β and TNF- α .

Periodontitis is accompanied by gingival bleeding and the production of an inflammatory exudate termed gingival crevicular fluid (GCF) that arises from the inflamed gingival tissues surrounding the teeth. GCF contains byproducts of connective tissue degradation, enzymes from host and bacterial cells, cytokines and other

inflammatory mediators, and has been studied for screening blood glucose and for biomarkers of both diabetes and periodontitis. Studies conducted to date suggest that gingival crevicular fluid may be an acceptable substitute for “finger stick” blood for determination of serum glucose levels and may therefore be a useful screening tool in the dental office. Although the ideal immune-inflammatory biomarker is yet to be found, some of the promising cytokines expressed in the GCF that are elevated in both periodontitis and diabetes include IL-1 β , IL-6, PGE₂, and VEGF. Further research is necessary to clarify the usefulness of these potential biomarkers and to likewise investigate additional cytokines which have to be studied in this regard.

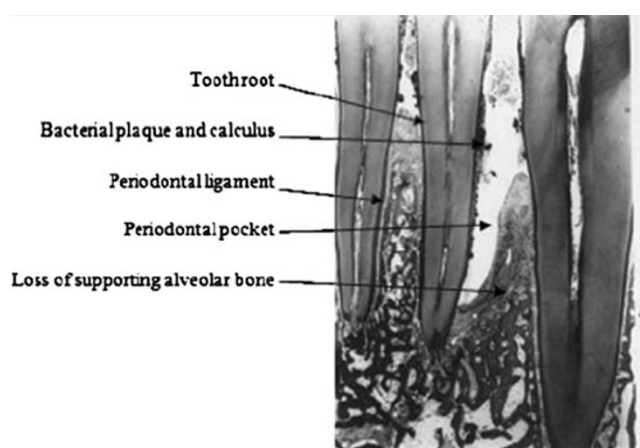


Fig. 1 Histology of periodontitis lesion. Bacteria-induced inflammation has resulted in loss of connective tissue attachment to the tooth, epithelial migration, pocket formation, and loss of supporting bone.

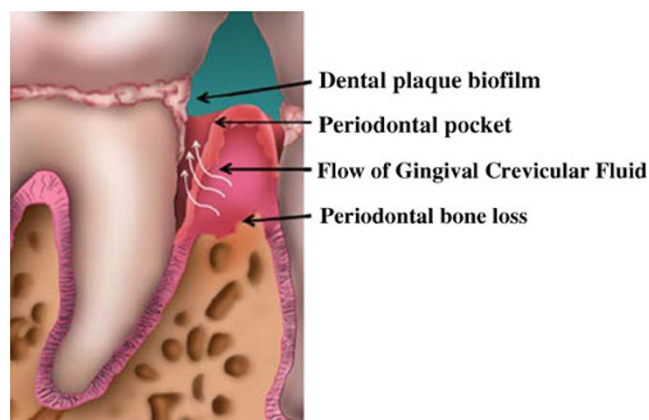


Fig. 2 Gingival Crevicular fluid flow in a periodontal pocket



Fig. 3 Clinical presentation of periodontitis in patient with undiagnosed diabetes mellitus (type 1). History of multiple recurring periodontal abscesses

ENDOTHELIAL DYSFUNCTION IN DIABETES: POTENTIAL APPLICATION OF CIRCULATING MARKERS AS ADVANCED DIAGNOSTIC AND PROGNOSTIC TOOLS

Abebe W, Mozaffari MS

Department of Oral Biology, College of Dental Medicine, Georgia Health Sciences University, Augusta, Georgia, USA

Diabetes mellitus is a common chronic metabolic disease with a growing prevalence rate worldwide. It is associated with vascular disorders, which contribute to as high as 80% of the 3.2 million annual deaths attributed to complications of diabetes. Endothelial dysfunction plays a crucial and an initiating role in vascular disorders in both type 1 and type 2 diabetes and insulin resistance/prediabetes. In the majority of diabetic cases, it precedes the development of overt hyperglycemia and its consequent complications. Assessing the status of the endothelium can serve as a valuable early diagnostic and prognostic tool for vascular diseases in diabetes. In human subjects, endothelial function/dysfunction has been evaluated using several *in vivo* techniques based on the measurement of the functional consequences of endothelial activity (i.e., relaxation/lumen size alterations in blood vessels). The commonly utilized techniques in this

regard are plethysmography, ultrasound and/or doppler designed to measure blood flow or lumen size in coronary arteries and peripheral blood vessels (e.g., brachial arteries). While these techniques are used primarily for research purposes, some of them appear to be clinically relevant for a limited scope of endothelial evaluations. However, certain limitations associated with the methods, particularly as related to technical difficulties and costs, have precluded their routine clinical applications.

Recently, a number of endothelial-derived circulating markers have been found to more directly indicate the status of the endothelium. The measurement of these biomarkers in the circulation is relatively easier and less costly. These potential circulating indicators include von Willebrand factor, soluble thrombomodulin, soluble E-selectin, asymmetric dimethylarginine, tissue plasminogen activator and endothelial microparticles. While the relative importance of each substance (or their combinations) for endothelial evaluation is not clearly defined, in most cases, the determination of these biomarkers has provided good indications of endothelial damage/activation, as it occurs in diabetes. However, the validity of measuring these biomarkers for diagnosis and/or prognosis of endothelial dysfunction and the associated vascular disorders in diabetes has not yet been fully established for routine clinical applications. Other potential indicators of endothelial function/dysfunction in diabetes are circulating endothelial cells and circulating endothelial progenitor cells. However, only very few studies have investigated the clinical application of these cellular biomarkers, suggesting the limited availability of information on their usefulness for diagnostic and/or prognostic purposes in human patients. Taken together, currently, the issue of circulating endothelial markers is an area of intense research interest with the potential to result in the development of clinically relevant assessment techniques of the status of the endothelium and the vasculature. It is hoped that as more research data become available, improved measurement of circulating endothelial indicators will make it possible to obtain valuable diagnostic and prognostic information on vascular events in diabetes and related conditions for routine clinical testing.

INFLAMMATORY MARKERS AS POTENTIAL PREDICTIVE INDICATORS FOR DIABETIC NEPHROPATHY

Baban B, El-Awady A, Yao Liu J, Mozaffari MS

Department of Oral Biology, College of Dental Medicine, Georgia Health Sciences University, Augusta, Georgia 30912, USA

Inflammatory pathways have emerged as major contributing mechanisms to the pathogenesis of insulin resistance/obesity/type 2 diabetes mellitus and associated chronic complications such as nephropathy. Thus, indices of inflammation that co-relate with disease progression could serve as potential predictive markers for the manifestation of target organ pathologies. Accordingly, the focus of our recent studies was to determine the impact of insulin resistance/type 2 diabetes on urinary, renal tissue and/or blood levels of inflammatory markers. For these studies we used two highly relevant animal models of the disease, namely the obese Zucker rat (OZR) and db/db mouse (and their respective lean nondiabetic controls, LZR and db/m, respectively); OZR and db/db mice lack the leptin receptor and thus are markedly obese, insulin resistant and hyperglycemic. The OZR displayed mild hyperglycemia but marked hyperinsulinemia in association with changes in urinary excretion and renal tissue levels of inflammatory markers including a) increased urinary monocyte chemoattractant protein-1 excretion and b) increased renal tissue levels of cyclooxygenase-2 and intercellular adhesion molecule-1 and c) increased renal tissue CD68 immunostaining. Subsequent studies using the severely hyperglycemic db/db mice revealed significant reduction in glomerular function but marked albuminuria compared to their lean db/m controls. Immunohistochemical studies revealed increased expression of interleukin (IL)-6 and IL-17 in renal tubules of db/db compared to their db/m controls. Flow cytometry studies further confirmed pro-inflammatory changes in db/db mice as indicated by increased IL-17 positive cells in peripheral blood and renal cells of db/db than db/m mice; the status of IL-23 is currently under investigation. Collectively, the results indicate that urinary and/or tissue as well as blood inflammatory markers can serve as potential predictive indicators for progression of type 2 diabetic nephropathy. Supported, in part, by a grant from the National Institutes of Health.

DRUG DELIVERY SYSTEMS: ADVANCED TECHNOLOGIES POTENTIALLY APPLICABLE IN PERSONALIZED TREATMENTS

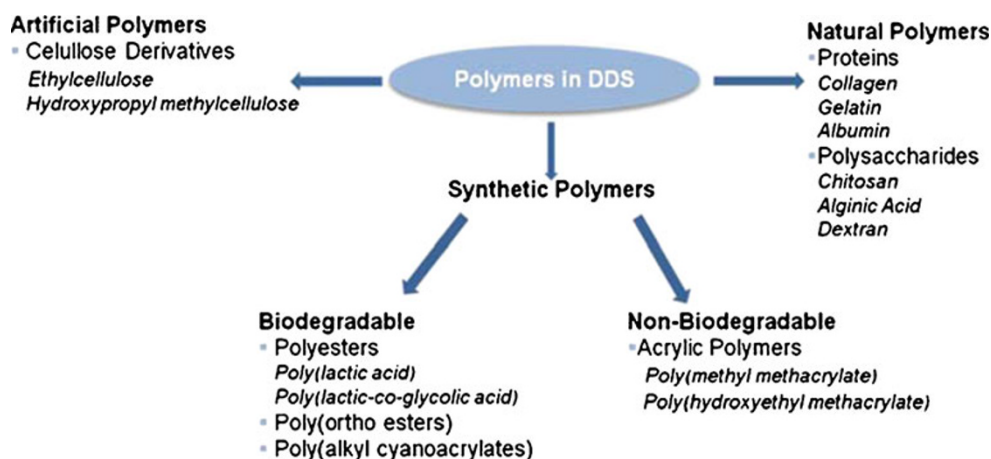
Coelho JF, Ferreira PC, Alves P, Cordeiro R, Fonseca AC, Góis JR, Gil MH

Department of Chemical Engineering, University of Coimbra, 3030–290 Coimbra, Portugal

Advanced drug delivery systems (DDS) present indubitable benefits for drug administration. Over the past three decades, new approaches have been suggested for the development of novel carriers for drug delivery. In this

presentation, general concepts and emerging research in this field based on multidisciplinary approaches aiming to create personalized treatment for a broad range of highly prevalent diseases (e.g., cancer and diabetes) will be presented. The information presented is organized in two parts. The first part provides an overview on currently available drug delivery technologies including a brief history on the development of these systems and some of

the research strategies applied. The second part provides information about the most advanced drug delivery devices using stimuli responsive polymers. Their synthesis using controlled-living radical polymerization strategy is presented. In a near future it is predictable the appearance of new effective tailor-made DDS, resulting from knowledge of different interdisciplinary sciences, in a perspective of creating personalized medical solutions.



Fig—Overview of the polymers used in DDS

CANCER PREDISPOSITION IN DIABETICS: RISK FACTORS CONSIDERED FOR PREDICTIVE DIAGNOSTICS AND TARGETED PREVENTIVE MEASURES

Cebioglu M, Schild HH, Golubnitschaja O

Department of Radiology, Rheinische Friedrich-Wilhelms-University of Bonn, Bonn, Germany

Cancer-related mortality in diabetics

According to the current worldwide statistics, every 10 seconds one patient dies on Diabetes mellitus (DM) related consequences. Once appeared, cancer outcomes have worse prognosis for diabetics compared to non-diabetic oncologic patients (Figure 1).

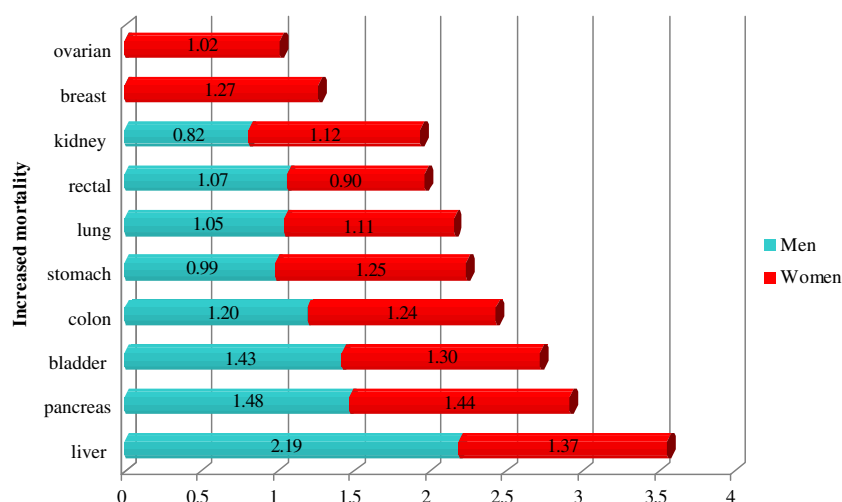


Fig. 1. Increased mortality of diabetics *versus* non-diabetics for single cancer types as documented for patients treated in USA in years 1982–1998. Data taken from [1]

The overall concept of cancer—predisposition in diabetics

Diabetics may be highly predisposed to cancer development specifically due to following contributors:

- strong stress factors (excessive metabolic alterations, disturbed glucose/insulin homeostasis, hormonal deregulation, insufficient detoxification) with consequently excessive production of ROS.
- mitochondrial dysfunction with consequent low energy production, insufficient repair capacity and accumulating damage to both chromosomal and mitochondrial DNA.
- high risk for infectious disorders with consequently induced viral proto-oncogenic activity as well as activity of particular pathogenic bacterial forms such as *Helicobacter pylori*.

Adequacy of stress response, repair capacity as well as immune defence are highly individual for each patient and strongly depend on risk factors such as genetic background, age, environmental factors, nutrition, body culture, life style, etc.

Outlook

Current biotechnology possesses sufficient power to estimate a severity of damage to sub-cellular structures, individual stress reactions and repair capacity. For example, by stress proteome profiling in peripheral leukocytes and blood plasma, individual stress reactions can be well estimated. Advanced predictive diagnostic approaches are currently close to clinical application and allow to select groups of risk and to estimate a predisposition to severe complications in diabetics. Much attention should be focused on targeted preventive arrangements in diabetes care, in order to restrict or even avoid severe secondary complications, such as cancer.

References

1. Cebioglu M, Schild HH, Lolubnitschaja O. Cancer predisposition in diabetics: risk factors considered for predictive diagnostics and targeted preventive measures. EPMA J. 2010;1:130–7.

BARIATRIC MEDICINE: MULTIDISCIPLINARY APPROACH FOR OBESITY PREVENTION

Dimitrov DV

Medical University Varna, Varna, Bulgaria

Obesity and its associated diseases are epidemic that represent a major threat to human health. In the last two decades an explosive increase in the number of people

diagnosed with diabetes has been observed worldwide and the global figure of affected individuals is expected to rise from currently 250 million to 350 million in 2025. The rapidly escalating number of affected patients at even very young age poses a tremendous burden on the public health system and a substantial reinforcement of research activities including transnational cooperation between scientists from different disciplines is urgently required to avoid a socioeconomic disaster. Dietary interventions and pharmacological strategies, however, failed to deliver success, due to side effects (e.g. sibutramine, rimonabant) or lack of efficacy (e.g. lorcaserin, recombinant leptin). For patients with obesity and type 2 diabetes, bariatric surgery is by far the most effective treatment—it is, indeed, the only form of treatment that can put patients into full long-term remission. This contribution reviews rise and fall of anti-obesity treatments and highlights the importance of bariatric surgery as the only way to cut diabetes costs at present. We discuss also public health implications. Until a successful non-surgical means for preventing and reversing obesity is developed, bariatric surgery appears to be the only intervention that can result in a sustained reversal of both obesity and type 2 diabetes mellitus in most patients receiving it. One of the key recommendations is the need for a multidisciplinary bariatric team to oversee the ongoing needs of patients after surgery, as well as to build a weight maintenance program. Beside surgeon, such **bariatric medicine team** should include metabolic physicians, nutritionists, physical activities specialists, cardiologists, etc.

MSCS AS TOOLS FOR RESTORING MORPHOFUNCTIONAL DEFICIENCY AND MODULATING IMMUNE RESPONSES AT THE PRECLINICAL STAGE OF T1D: MILESTONES AND HANDICAPS

Kostyushev DS¹, Paltsev MA², Suchkov SV^{1,3}

¹I.M. Sechenov First Moscow State Medical University, Moscow, Russia

²National Research Center “Kurchatov Institute”, Moscow, Russia

³Moscow State Medical Dentistry University, Moscow, Russia

Type 1 Diabetes (T1D) is a progressive autoimmune disease associated with reduction of beta cell mass and, as a consequence, metabolic disturbances in peripheral blood glucose levels. Early diagnosis of T1D at the pre-diabetic stage allows for timely implementation of efficient preventive and predictive measures including cell-based technologies aimed at stabilization of the patient's immune status and reseeded the pancreas with newly formed beta cells. Mesenchymal Stem Cells

(MSCs) are among the most promising therapeutic tools for repairing the architectonics of the pancreas through secretion of a vast majority of paracrine factors or directed trans-differentiation into beta cells. In addition, MSCs improve immune responses by acting upon the T cell link of immunity (increasing the population of CD4+CD25+ FoxP3+ Tregs and Th2 and decreasing the population of Th1), prevent the presentation of antigens by expressing negative co-stimulatory molecules (PD-L1, PD-L2), induce revascularization of the pancreas and afford effective anti-apoptotic protection of beta cells. The most promising approaches to isolation of MSCs, their targeted delivery by directed homing, effects of secreted soluble factors on pancreas regeneration and ways to increase the proliferative activity of MSCs through induction of expression of a vast array of humoral factors are considered. The totality of experimental data on tumorigenesis in animal models after MSCs injection is discussed in terms of their significance and possibility of their extrapolation to human beings. This contribution deals with the most promising approaches to preventing malignant growth in human beings following MSCs injection.

POLYMORPHIC GENETIC MARKERS ARE OF SIGNIFICANCE FOR MONITORING OF DISEASE PROGRESSION IN METABOLIC SYNDROME PATIENTS

Voytovich AN¹, Bogdanova MA¹, Romashkina OS¹, Bystrova AA², Smirnov BI³, Smirnov AM⁴, Demin GS⁴, Krasilnikova EI², Berkovich OA², Shliakhto EV², Larionova VI¹

¹St. Petersburg State Pediatric Medical Academy, Saint-Petersburg, Russia

²St. Petersburg State Pavlov Medical University, Saint-Petersburg, Russia

³St. Petersburg State Electrotechnical University, Saint-Petersburg, Russia

⁴Gene Ltd, Saint-Petersburg, Russia

Background: The metabolic syndrome (MS) is a cluster of metabolic abnormalities, such as abdominal obesity, arterial hypertension, and atherogenic dyslipidaemia, which are associated with development of secondary complications such as type 2 diabetes (DM2). Recently, many studies showed pathology-specific polymorphisms in apolipoprotein genes that might be associated with the development of DM2.

Objective: To study a possible association of several polymorphisms of apo-genes *APOA1* G-75A, *APOA1* C83T, *APOC3* SstI, *APOE* epsilon, *APOA5* T-1131C, and *APOA5* S19W with DM2 in MS patients.

Study population: MS patients with DM2, including 100 males and 264 females, average age 50.9±0.5, and controls, including 114 healthy males (average age 40.0±0.5) and 84 females (average age 85.9±0.5). All of them were examined clinically, biochemically and genetically. **Results:** Among male MS patients with DM2, there was a higher rate of carries of APOE e2-allele compared to the controls (22% vs. 13%, p=0.067). In addition, male patients demonstrated a higher rate of carries of APOA5 19W-allele compared to the controls (13% vs. 3%, p=0.005). There was not a significant difference in genotype distribution of the studied apo-genes between female groups. All studied groups were shown to correspond to Hardy-Weinberg equilibrium.

Conclusion: Gender (male) is considered as a risk factor in a diseases progression. Our results suggest that the APOE and APOA5 S19W polymorphisms are of significance in male patients with DM2.

ASSOCIATION OF ACE I AND FABP2 GENES POLYMORPHISM IN CASES WITH TYPE-2 DIABETES MELLITUS IN NORTHERN INDIA

Mahdi F¹, Banerjee D¹, Rizvi N³, Sapkota R², Saxena S³, Khan NA², Raza ST¹

¹Era's Lucknow Medical College & Hospital, Lucknow, India.

²Baba Farid Institute of Technology, Dehradun, India.

³Amity Institute of Biotechnology, Amity University, Lucknow, India

Background: India has the world's largest diabetes population with an estimated 50.8 million people living with type 2 Diabetes Mellitus. Type 2 DM can shorten the normal lifespan of an individual by up to one-fifth and is a complex disorder accounting for 90–95% of all diabetes syndromes. Diabetes mellitus has a major impact on the cardiovascular and renal system, with the main cause of death being directly related to cardiovascular disease.

Angiotensin Converting Enzyme (ACE I), a key enzyme in the renin-angiotensin system, is a zinc metallopeptidase, which catalyses the conversion of Angiotensin I to Angiotensin II, a potent vasoconstrictor, and through protease activity it also inactivates bradykinin, a potent vasodilator. Insertion/deletion (I/D) polymorphism of a 287 bp *Alu* repeat sequence in intron 16 of the ACE gene is strongly associated with plasma and cellular ACE levels and it indicates that the polymorphism may modulate the expression of the ACE gene.

Fatty acid-binding protein (FABP2) is involved in the transport and metabolism of saturated and unsaturated long-chain fatty acids. The FABP2 gene has been proposed as a

candidate gene for diabetes because the protein it codes for is involved in Fatty Acid absorption and metabolism and therefore, affect insulin sensitivity and glucose metabolism. The Ala54Thr polymorphism is the most extensively studied FABP2 variant, as this variant seems the most likely candidate to alter the protein's function.

Material & Methods: Polymerase Chain Reaction—Restriction Fragment Length Polymorphism (PCR-RFLP) and Genotyping was done to determine the ACE and FABP2 gene polymorphism in 75 cases and 57 controls.

Results: The mean age of cases ($n=75$) in the study group was (48.29 ± 11.89) years while in the control group ($n=57$) was (31.03 ± 7.38) years. The frequencies of the genotypes DD, ID and II in the T2DM group were 16%, 55% and 29% respectively while in the control group these frequencies were 20%, 78% and 2%. The frequency of I and D allele in the T2DM patients group was 57% and 43% respectively as compared to 51% and 49% in the controls. I/D genotype were significantly more frequent in healthy controls while I/I genotype occurred with significantly more frequency in patients with T2DM. The frequencies of the genotypes Ala54Ala, Ala54Thr and Thr54Thr in the T2DM group were 17%, 63% and 20% respectively while in the control group these frequencies were 23%, 63% and 14%. The frequency of Ala54 and Thr54 allele in the T2DM patients group was 48% and 52% respectively as compared to 54% and 46% in the controls. FABP2 gene polymorphism shows no significant difference in Genotypes and allele frequencies found in cases and controls.

Conclusion: It seems that the I/I allele frequency of ACE I/D gene polymorphism was significant in the T2DM cases as compared to controls. While the FABP2 gene polymorphism shows no significant difference in Genotypes and allele frequencies found in cases and controls. It might be recommended that ACE gene I/D polymorphisms can be a good marker for the early identification of population at risk of Type 2 diabetes mellitus.

MEASUREMENT OF ANGIOGENESIS PROMOTORS AND CYTOKINES CONCENTRATIONS IN INTRAOCULAR FLUID OF PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY FOR TREATMENT TAILORING POSSIBILITY

Ůřalová J, Kozová M, Rusnak S, Ricarova R, Topolcan O
Immunanalytic Laboratory and Eye Department of University Hospital and Medical Faculty in Pilsen, E. Benese 13, 305 99 Plzen, Czech Republic

Introduction: Proliferative Diabetic Retinopathy (PDR) is the most common diabetic eye disease. It is caused by pathology-specific changes in the blood vessels of the retina.

It is a leading cause of blindness in adults that can affect both central and peripheral vision. Vision loss can be reduced by timely diagnosis and treatment. Nowadays ophthalmology is based on determination of status quo solely by visual control or imaging techniques. Our aim was to prove the suitability of multiplex analysis for measurement of changes of cytokines and angiogenetic factors in intraocular fluid of patients with proliferative diabetic retinopathy (PDR) and to determine its clinical applicability for a potential use in ocular medicine.

Patient cohort: Patients with proliferative diabetic retinopathy, patients with retinal detachment and control group of patients before cataract surgery without any ocular pathology were examined.

Methods: Intraocular fluid samples were aspirated from anterior chamber of patients with PDR.

Concentrations of IL8, VEGF, EGF, IL 6, IP10, MCP1, PDGF, Rantes, BDNF, CNTF, TGF β 1 and IL 10 were measured simultaneously in intraocular fluid using multiplex panel kits from Millipore (USA) and Luminex 100 instrument (Luminex corp., USA). Levels of biomarkers were compared between groups by Wilcoxon test and ROC analysis was performed.

Results: We were able to detect levels of EGF, IL6, VEGF, BDNF, CNTF, IL8, IP10, MCP1, PDGF AA, and TGF β . In PDR patients, VEGF and other angiogenetic factors and antiangiogenetic factor (IP 10) were found to be higher in intraocular fluid compare to controls. In retinal detachment patients, intraocular levels of inflammatory markers were observed to be higher compare to controls.

Conclusion: Multiplex analysis enables an easy simultaneous measurement of multiple markers in a very small sample volume and so enables the use of biomarker analyses in intraocular fluid as a standard method.

Support: Study was supported by the study project NS10251-3.

NUTRITION OF PATIENTS WITH DIABETES MELLITUS TYPE 2 IN RELATION WITH SMOKING ADDICTION—SURVEY POST-MONICA 2008/2009 IN CZECH REPUBLIC

Galovcová M, Adámková V, Cífková R, Petržílková Z, Bruthans J, Lánská V

Department of Preventive Cardiology, Institute for Clinical and Experimental Medicine, Prague

Introduction: Tobacco smoking is one of the most important risk factors for cardiovascular disease (CVD). Smokers have 2-fold higher risk of coronary heart disease, 95% contributes to a higher incidence of peripheral arterial disease. Smoking affects not only alone, but synergistically with other risk factors that potentiate the overall effect. The combination of

smoking diabetics is a particular risk factor. However, stop smoking is not a simple process: the main role plays strong motivation. Some smokers argue with weight reduction. Are smoking diabetics really slimmer?

Objective: To compare nutritional parameters in smokers and nonsmokers diabetics type 2.

Methods: 1% random population sample aged 25–64 years was selected from nine districts of the Czech Republic. The examination consisted of completing a standard questionnaire, obtaining major anthropometric data, repeated blood pressure measurements, and blood sampling.

Results: We examined 3612 persons, whom 250 were type 2 diabetics from.

The experimental group included 162 (64.8%) male and 88 (35.2%) female diabetics.

Therefrom, smokers were 52 (32%) men and 20 (23%) women. The average age of smokers was 54.4 ± 8.6 years and 56.6 ± 7.0 years of non-smokers ($p < 0.05$).

	SMOKERS	NON-SMOKERS	P
Age	54.4 ± 8.6	56.6 ± 7.0	*
sBP	136.8 ± 19.6	138.9 ± 20.0	n.s.
dBp	84.3 ± 11.6	82.8 ± 10.2	n.s.
BMI	31.8 ± 6.1	33.1 ± 5.8	n.s.
Waist	105.9 ± 14.6	108.0 ± 13.6	n.s.
TC	5.0 ± 1.2	5.2 ± 1.4	n.s.
TAG	2.4 ± 1.6	2.4 ± 1.9	n.s.
HDL-chol.	1.2 ± 0.4	1.2 ± 0.3	n.s.
LDL-chol.	2.8 ± 1.0	3.0 ± 1.1	n.s.
Glucose	8.6 ± 3.0	9.1 ± 3.0	n.s.

We found no indication that smoking diabetics have smaller BMI and waist. However, both groups demonstrated poorly controlled diabetes and higher blood pressure compared to non-smoking diabetics.